REMARKS

Introductory Matter

Applicants thank Examiner Schnizer for discussing the October 12, 2005 Office Action and possible claim amendments with applicants' representatives, Ms. Li and Mr. Roise, by telephone on March 30, 2005.

Claim Amendments

Claims 1–24 and 51–79 were under consideration in the October 12, 2004 Office Action. Claims 25–50 were withdrawn in a previous Office Action.

Claims 1 and 9, and the claims dependent therefrom, are amended to recite that the transgenic mammal, progeny, or embryo thereof is a "transgenic rodent, progeny, or embryo thereof". Applicants have amended claim 19, and the claims dependent therefrom, to recite that the animal organ or region thereof is a "rodent organ or region thereof". Applicants have amended claim 72, and the claims dependent therefrom, to recite that the live animal, organ or tissue of the live animal is a "live rodent, organ or tissue of the live rodent". Support for these amendments can be found throughout the specification, e.g., at page 6, line 26, at page 7, line 2, in Examples 2–4, and at claims 4 and 12, as originally filed.

Claims 1, 9, 18, 19, and 72, and the claims dependent therefrom, are amended to specify that the DNA comprises a "gene coding for an enhanced green fluorescent protein". Support for these amendments can be found, e.g., at specification page 10, line 25–page 11, line 11, page 16, lines 20–26, and in Examples 3 and 4.

Claim 1, and the claims dependent therefrom, are amended to specify that the fluorescence of the enhanced green fluorescent protein is detected "in the rodent, progeny or embryo thereof". Claim 9, and the claims dependent therefrom, are amended to specify that the fluorescence of the enhanced green fluorescent protein is detected "in the rodent". Claim 19, and the claims dependent therefrom, are amended to specify that the fluorescence of the enhanced green fluorescent protein is detected "in the rodent organ or region thereof". Claim 72, and the claims dependent therefrom, are amended to specify that the fluorescence of the enhanced green fluorescent protein is detected "in the live transgenic rodent, or in the organ, tissue or region of the live transgenic rodent". Support for these amendments can be found, e.g., at specification page 12, line 21–page 13, line 2, page 16, lines 21–26, page 23, lines 18–21, and page 25, lines 10-13.

Claims 4, 5, and 13 are amended to add the article "a".

Claim 8 is amended to depend from claim 1 and to clarify the antecedent basis for the claim.

Claim 9 is amended to delete the word "selectively".

Claim 16 is amended to depend from claim 9 and to clarify the antecedent basis for the claim.

Claim 18 is amended for clarity.

Claim 24 is amended to depend from claim 19 and to clarify the antecedent basis for the claim.

Claim 77 is amended to clarify the antecedent basis for the claim.

Claims 6–7, 14–15, 22–23, 51–71, 75–76, and 78–79 are hereby canceled.

No new matter is added by these amendments. Their entry is respectfully requested. Cancellation of any subject matter by amendment is expressly without waiver of applicants' right to claim such subject matter in one or more continuing applications.

Drawings

The drawings are objected to as indicated in Form PTO 948 accompanying the Office Action mailed October 4, 2000. Applicants stand ready to provide formal drawings should claimed subject matter be found allowable.

Rejections Withdrawn

Applicants acknowledge with appreciation the withdrawal of the rejection of claims 58–65 under 35 U.S.C. § 112, ¶ 2.

Claim Objections

Claim 4 is objected to for lack of an article preceding "mouse". This objection is obviated by amendment of the claim to recite "a mouse". Withdrawal of the objection is requested.

Claims 5, 13, and 61 are objected to for lack of an article preceding "rat nestin gene". These objections have been obviated by amendment of claims 5 and 13 to recite "a rat nestin gene" and mooted by cancellation of claim 61. Withdrawal of the objection is requested.

Claims 6, 7, 14, 22, 55, 56, 62, 69, and 75 are objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. These objections are moot in light of the cancellation of these claims.

Claim 10 is objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant has amended claim 9 to delete the word "selectively", thereby obviating the objection. Withdrawal of the objection is requested.

Claim Rejections Under 35 U.S.C. § 112, 1st - New Matter¶

Claims 15, 16, 23, 24, 63, 64, 70, 71, and 76 stand rejected for failing to comply with the written description requirement. Cancellation of claims 15, 23, 63, 64, 70, 71, and 76 renders the rejection moot with respect to these claims. Amendment of the dependencies of claims 16 and 24 obviates the rejection with respect to these claims. Withdrawal of the rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, 1st ¶ - Scope of Enablement

Claims 1–17, 19–24, and 51, 53–58, 60–66, 68–77, and 79 stand rejected as not reasonably proving enablement for non-mouse transgenic mammals, progeny, or embryos. This rejection is moot with respect to claims 6–7, 14–15, 22–23, 51, 53–58, 60–66, 68–71, 75–76, and 79, which are hereby canceled. Applicants traverse the rejection with respect to claims 1–5, 8–13, 16–17, 19–21, 24, 72–74, and 77. Solely to

further prosecution, however, applicants have amended claims 1–5, 8–13, and 16–17 to recite that the transgenic mammal, progeny, or embryo is a transgenic rodent, progeny, or embryo. Applicants have amended claims 19–21, and 24 to recite that the animal organ or region thereof is a rodent organ or region thereof. Applicants have amended claims 72–74 and 77 to recite that the live animal, organ or tissue of the live animal is a live rodent, organ or tissue of the live rodent. Applicants maintain that the specification clearly enables a person of skill in the art to make and use the full scope of the invention as currently claimed. Withdrawal of the rejection is respectfully requested.

Claims 19–24 and 72–77 stand further rejected as nonenabled because, according to the Examiner, the specification fails to teach how to use transgenic mammals expressing GFP in multipotent precursor or stem cells to measure any population of cells in a non-mammal. This aspect of the rejection is moot with respect to claims 22–23 and 75–76, which are hereby canceled. Applicants traverse with respect to claims 19–21, 24, 72–74, and 77. Solely to further prosecution, however, applicants have amended the preamble of these claims to recite that measurement is in a rodent. Withdrawal of the rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, 2nd ¶ - Indefiniteness

Claims 16, 24, 64, and 71 stand rejected as indefinite because they recite "the promoter" without antecedent basis. Applicants have amended the dependencies of claims 16 and 24, thereby obviating the rejection with respect to those claims. Applicants

have canceled claims 64 and 71, thereby rendering moot the rejection with respect to those claims. Applicants request that the rejection be withdrawn.

Claim Rejections Under 35 U.S.C. § 102(b) - Anticipation

Claims 1–14, 17, 19–22, 51–62, 65–69, 78, and 79 stand rejected as being anticipated by Zimmerman (1994), as evidenced by Hogan (1996). According to the Examiner, Zimmerman teaches transgenic mice comprising a lacZ transgene under the control of the promoter and second intron enhancer of the rat nestin gene. The Examiner notes that the beta galactosidase disclosed by Zimmerman comprises 38 tryptophan residues and is therefore a fluorescent protein. The Examiner asserts that one of ordinary skill in the art could detect the beta galactosidase by fluorescence in various ways, and that Zimmerman thus anticipates the claims.

Applicants have canceled claims 6–7, 14, 22, 51–62, 65–69, and 78–79, thereby mooting the rejections with respect to these claims. Applicants have amended the other rejected claims to recite that the protein encoded by the transgene is an "enhanced green fluorescent protein" and that the fluorescence of the protein is detected either "in the rodent, progeny or embryo thereof", "in the rodent", or "in the rodent organ or region thereof". Applicants maintain that Zimmerman, either alone, or as evidenced by Hogan, fails to teach the use of an enhanced green fluorescent protein or the measurement of protein fluorescence in a rodent and that it therefore fails to anticipate the amended claims. Applicants respectfully request that the rejection be withdrawn.

Claim Rejections Under 35 U.S.C. § 103(a) - Obviousness

Claims 1–15, 17, 18–22, 24, 51–63, 65–69, 78, and 79 stand rejected as obvious over Zimmerman (1994) in view of Chiochetti (1997). According to the Examiner, Zimmerman teaches transgenic mice comprising a construct containing a lacZ reporter transgene under the control of the promoter and second intron enhancer of the rat nestin gene. According to the Examiner, beta galactosidase was expressed in neuronal stem cells of the resulting animals, and allowed measurement of these cells. The Examiner concedes that Zimmerman does not teach a construct comprising green fluorescent protein. The Examiner asserts, however, that Chiochetti teaches that green fluorescent protein is a more powerful and sensitive tool for studying gene expression in transgenic animals than is beta galactosidase, and that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Zimmerman by substituting green fluorescent protein for beta galactosidase and to study gene expression in neuronal stem cells in living animals and their organs and tissues. According to the Examiner, there was motivation to combine these references because Chiochetti teaches that green fluorescent protein is a more powerful and sensitive tool for studying gene expression in transgenic animals than is beta galactosidase.

Applicants have canceled claims 6–7, 14–15, 22, 51–63, 65–69, 78, and 79, thereby mooting the rejections with respect to these claims. As described above, applicants have amended the other rejected claims to recite that the fluorescent protein

encoded by the transgene is an "enhanced green fluorescent protein" and that the fluorescence of the protein is detected either "in the rodent, progeny or embryo thereof", "in the rodent", or "in the rodent organ or region thereof".

Applicants maintain that Zimmerman fails to teach or suggest the use of any type of fluorescent protein for the measurement of gene expression, either indirectly, or through the measurement of protein fluorescence in a rodent. Applicants likewise respectfully maintain that Chiocchetti fails to provide the necessary teaching and motivation to overcome the defects of Zimmerman. Chiocchetti teaches the use of *unmodified* green fluorescent protein from *Aequorea victoria* as a reporter of gene expression in fixed tissue sections and liver homogenates from transgenic mice. Chiocchetti also references the use of green fluorescent protein to measure gene expression in living tissues of *transparent* organisms, such as *Drosophila* and *Dictyostelium*. Chiocchetti does not, however, teach or suggest that an *enhanced* green fluorescent protein may be used to detect gene expression in a *non-transparent* transgenic animal, such as a transgenic rodent. Applicants maintain that the combination of Chiocchetti and Zimmerman does not, therefore, render the amended claims obvious under 35 U.S.C. § 103(a).

Claims 1–15, 17–22, 24, 51–63, 65–69, 72–75, and 77–79 also stand rejected as obvious over Zimmerman (1994) in view of Yamaguchi et al. (1998). The Examiner's characterization of Zimmerman is described above. According to the

Examiner, Yamaguchi teaches adult transgenic mice comprising a green fluorescent protein gene under the control of a nestin promoter. The Examiner asserts that Yamaguchi teaches that neuronal stem cells could be easily visualized in vivo in the mice but is silent as to the nature of the regulatory control regions present in the promoter. According to the Examiner, it would have been obvious to modify the method of Zimmerman by substituting green fluorescent protein for beta galactosidase and to study gene expression in neuronal stem cells in living animals and their organs and tissues. According to the Examiner, motivation to combine is provided because Yamaguchi teaches that green fluorescent protein allows visualization of neuronal stem cells in vivo, and that study of such cells in vivo would lead to an understanding of the process of organization and plastic changes of the neuronal circuit during development and in adults.

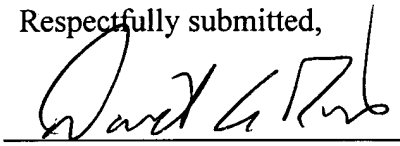
Applicants have canceled claims 6–7, 14–15, 22, 51–63, 65–69, 75, and 78–79, thereby mooting the rejections with respect to those claims. As described above, applicants have amended the other rejected claims to recite that the fluorescent protein encoded by the transgene is an "enhanced green fluorescent protein" and that the fluorescence of the protein is detected either "in the rodent, progeny or embryo thereof", "in the rodent", "in the rodent organ or region thereof", or "in the live transgenic rodent, or in the organ, tissue or region of the live transgenic rodent".

Applicants maintain that Zimmerman fails to teach or suggest the use of any type of fluorescent protein for the measurement of gene expression, either indirectly, or through the measurement of protein fluorescence in a rodent. Applicants also respectfully maintain that Yamaguchi does not teach or suggest that an *enhanced* green fluorescent protein may be used to detect gene expression *within* a transgenic animal, such as a transgenic rodent. Applicants maintain that the combination of Yamaguchi and Zimmerman does not, therefore, render the amended claims obvious under 35 U.S.C. § 103(a). Applicants therefore respectfully request that the rejection be withdrawn.

CONCLUSION

In light of the foregoing amendments and remarks, applicants request that the Examiner withdraw all outstanding rejections and grant allowance of the pending claims. The Examiner is invited to telephone the undersigned to resolve any remaining issues in this application.

Respectfully submitted,



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